

Expert Opinion

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Organogels in drug delivery

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In the last decade, interest in physical organogels has grown rapidly with the discovery and synthesis of a very large number of diverse molecules, which can gel organic solvents at low concentrations. The gelator molecules immobilise large volumes of liquid following their self-assembly into a variety of aggregates such as rods, tubules, fibres and platelets. The many interesting properties of these gels, such as their thermoreversibility, have led to much excitement over their industrial applications. However, only a few organogels are currently being studied as drug/vaccine delivery vehicles as most of the existing organogels are composed of pharmaceutically unacceptable organic liquids and/or unacceptable/untested gelators. In this paper a brief overview of organogels is presented, followed by a more in-depth review of the gels that have been investigated for drug and/or vaccine delivery. These include microemulsion-based gels and lecithin gels (studied for transdermal delivery), sorbitan monostearate organogels and amphiphilogs (studied as vaccine adjuvants and for oral and transdermal drug delivery, respectively), gels composed of alanine derivatives (investigated as *in situ* forming gels) and Eudragit organogels (studied as a matrix for suppositories). Finally, pluronic lecithin organogels, descendants of lecithin gels but which are not really organogels, are briefly discussed for their interesting history, their root and the wide interest in these systems.

Keywords: drug delivery, organogel, organogelator, vaccine delivery

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1. Introduction

It has been said that gels are easier to recognise than to define [1], and a number of definitions have been proposed to reduce the indiscriminate use of the term 'gel' [2-4]. A simple working definition of the term 'gel' is a soft, solid or solid-like material, which contains both solid and liquid components, where the solid component (the gelator) is present as a mesh/network of aggregates, which immobilises the liquid component. The solid network prevents the liquid from flowing, primarily via surface tension. The gel is said to be a hydrogel or an organogel depending on the nature of the liquid component: water in hydrogels and an organic solvent in organogels. Gels can also be classified according to the bonds present in the gelator network: physical gels are held by weaker physical forces of attraction such as van der Waals interactions and hydrogen bonds, whereas chemical gels are held by covalent bonds.

Hydrogels (composed of water held by a three-dimensional polymeric network) have been extensively studied as vehicles for a wide range of drugs. They have been fabricated in a variety of different shapes (e.g., rods, disks, films and microparticles) depending on the intended applications and sites of administration. In addition, some thermoresponsive gels can be administered parenterally as a liquid, which forms a gel *in situ* at body temperature. In contrast to hydrogels, research into organogels for drug delivery began fairly recently. In the last decade or so interest in physical organogels increased dramatically, with the (often, serendipitous) discovery and synthesis of a very large number of diverse molecules that are able to gel a range of



organic solvents at low concentrations (typically a few weight percent). Examples of gellable organic solvents include aliphatic and aromatic hydrocarbons, alcohols, silicone oil, dimethyl sulfoxide and vegetable oils. In contrast to hydrogels, in which the gelator is normally a polymer, most of the organogelators are relatively small molecules (MW ~ 3000 Da) and they have been called low molecular weight organogelators (LMOGs). The latter and related organogels have been reviewed by a number of authors [5-10] and will only be briefly discussed in this paper to put their applications in drug delivery into context.

1.1 Organogelators

The simplest organogelators are n-alkanes (C = 24, 28, 32, 36), which gel other relatively short chain n-alkanes such as hexadecane and other organic liquids [11]. Other examples of organogelators include substituted fatty acids [12] (e.g., 12-hydroxyoctadecanoic acid); 1,3:2,4-di-O-benzylidene-D-sorbitol (D-DBS) [13]; sorbitan monostearate, a non-ionic surfactant [14]; steroids and their derivatives [15]; anthryl derivatives (e.g., 2,3-bis-n-decyloxyanthracene [16]); macrocyclic gelators (e.g., calixarenes [17]); ALS compounds (an aromatic moiety attached to a steroidal group by a linker segment) [18]; cyclo(dipeptide)s [19]; bisurea compounds [20]; bisamides [21]; bolaform amides derived from amino acids [22]; n-alkyl perfluoroalkanamides [23]; carbohydrate derivatives [24]; perfluoroalkanes, which gel liquid carbon dioxide [25], a mixture of highly reactive methyl 2,6-diisocyanatohexanoate and alkylamines in an organic solvent, which react when mixed to form a product that gels the organic solvent [26]; primary alkyl amines, which gel organic solvents following the uptake of CO₂, NO₂, SO₂ or CS₂ [27]; light-responsive gelators, which produce gels whose sol-to-gel transition may be switched by irradiation with UV and visible light [28]; oxadiazole-based benzene 1,3,5-tricarboxamide, a non-fluorescent gelator, which produces highly fluorescent organogel [29]; cobalt (II) triazole complexes, which, unlike most organogels, form gels at high temperatures and solutions at low temperatures [30]; and fatty acid derivative of L-alanine, which selectively gels the organic solvent but not the aqueous phase when added to an oil/water mixture [31]. Certain compounds can only gel organic solvents in the presence of other compounds, for example, aminopyrimidine and dialkylbarbituric acid gel cyclohexane when present at 1:1 molar mixtures [32]. The chemical structures of some of these gelators are shown in Figure 1; one can see that organogelators are diverse in nature and it is not possible, so far, to predict whether a molecule will gel organic solvents. As mentioned earlier, the ability of many of these compounds to gel organic liquids was discovered by chance. Subsequently, many more compounds related to the organogelators have been synthesised to produce libraries of gelators in an attempt to understand the chemical moieties needed for gelation, the forces of attraction involved in gelation and the mechanisms of gelation.

1.2 Gel preparation

Most organogels are prepared by heating a mixture of the gelator and the liquid component to form an organic solution/dispersion, followed by cooling of the latter, which sets into a gel. Heating allows dissolution of the gelator in the liquid. Following cooling, the solubility of the gelator in the liquid phase decreases, and gelator-solvent interactions are reduced, which results in the gelator molecules 'coming out' of solution. Gelator-gelator interactions lead to gelator self-assembly into well-defined aggregates such as tubules, rods and fibres. Entanglement of the aggregates and connections among them result in the formation of a three-dimensional network, which immobilises the fluid phase (i.e., a gel is formed). The three-dimensional network acts as the gel skeleton and confers strength and resilience to the gel. Connections among gelator aggregates are important for gel formation; in their absence, the gel state may be lost even if numerous gelator aggregates are present. A few examples of gelator aggregates and three-dimensional networks are shown in Figures 2.

The physical organogels, held together by noncovalent forces, are thermoreversible; that is, following heating, the gel melts to the sol phase as the gelator aggregates dissolve in the organic liquid, whereas cooling the hot sol phase results in gelation. One can see the requirement for gelator solubility in the liquid at high temperature but insolubility at lower temperatures, for gelation. The temperature at which the sol-to-gel or gel-to-sol transition occurs is called the gelation temperature (T_g). The latter is usually broad, over a few degrees Celsius, as a number of events occur at the transition; for example, the breakup of the connections between gelator aggregates and the dissolution of individual aggregates. Different methods have been used to measure T_g; for example, differential scanning calorimetry, rheological measurements, melting point apparatus, hot-stage light microscopy (when gelator aggregates are large enough to be visible with light microscopy) and 'falling drop' method. These methods often give slightly different values for T_g because different events are monitored [33,34]. For example, when the melting point apparatus or 'falling drop' method is used, the temperature at which the gel flows is measured; gelator aggregates and aggregate-aggregate interactions may still be present. In contrast, when the hot-stage light microscopy is used, the operator may record the temperature at which all the gelator aggregates have disappeared. In addition, the T_g found by heating the gel to the sol phase or cooling the sol to the gel state differ slightly. The gel T_g is usually lower than the melting point of the neat gelator; for example, the T_g of a 10% weight-to-volume (w/v) sorbitan monostearate/hexadecane gel was found to be 41 – 44°C, compared with 51°C for the melting point of neat sorbitan monostearate [14].

In contrast to the gel preparation described above, a number of organogels are prepared by the addition of a third component to an organic solution; for example, an organic solution of *bis*-(2-ethylhexyl) sodium sulfosuccinate (AOT)

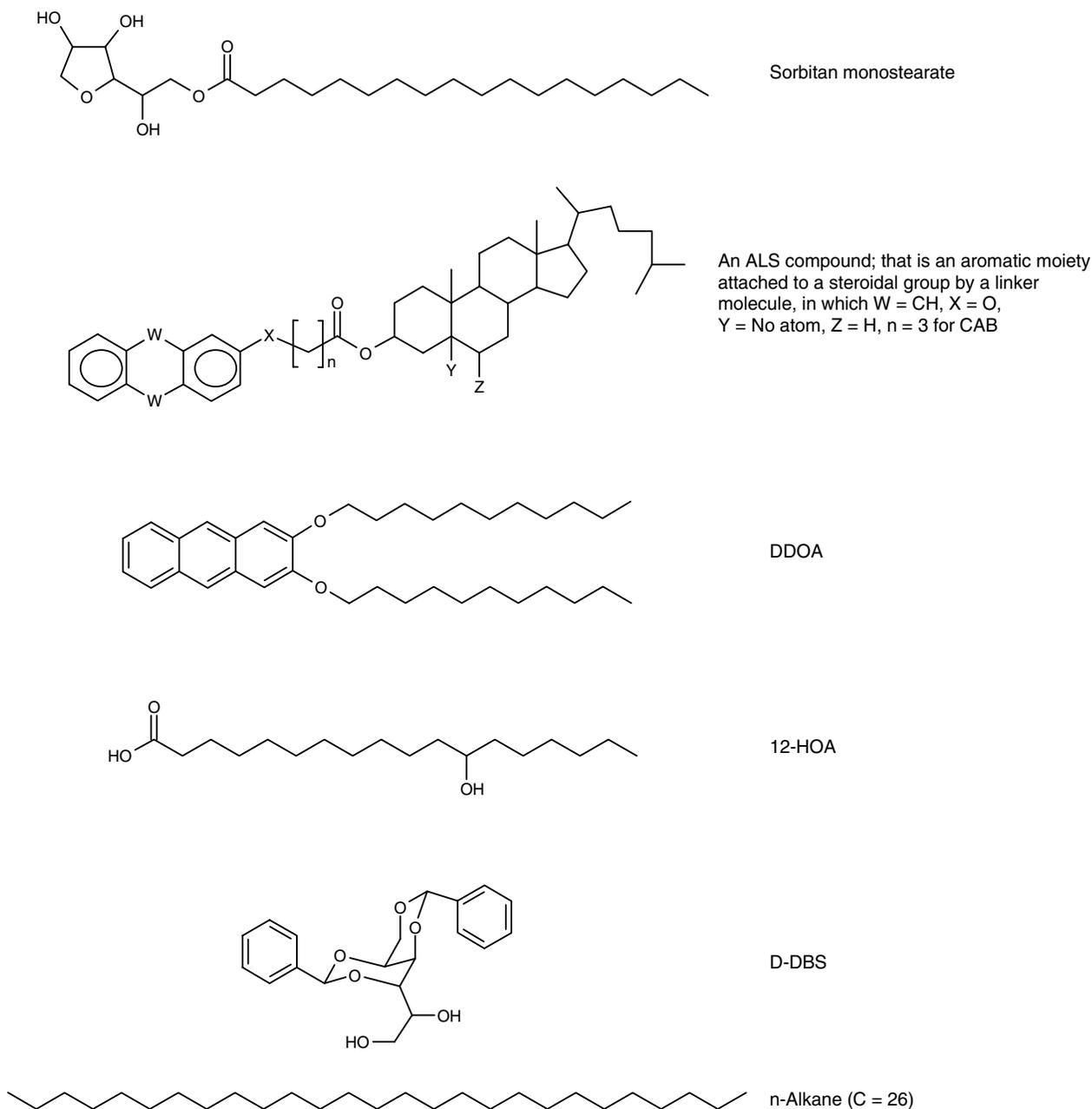


Figure 1. The chemical structures of a few organogelators.

CAB: Cholesterol 4-(2-anthryloxy)butanoate; D-DBS: 1,3:2,4-di-O-benzylidene-d-sorbitol; DDOA; 2,3-bis-n-Decyloxyanthracene; 12-HOA: 12-Hydroxyoctadecanoic acid.

can be gelled by the addition of phenolic species [35,36]. Solutions of lecithin in an organic solvent such as iso-octane can be gelled by the addition of trace amounts of a polar substance; for example, water, glycerol, ethylene glycol or formamide [37,38]. Complex organogels have also been prepared by the gelation of a water-in-oil (w/o) microemulsion using gelatin: a hydrogelator [39].

A simple visual test to determine whether gelation has taken place involves inverting the reaction vessel; gelation is said to have occurred if the sample does not flow. Rheological

measurements provide a more objective diagnosis of gelation. The gels formed can be characterised in terms of the concentration of gelator required to immobilise the liquid, the gel's rheology, lifetime (the period of time that gels can remain intact when stored in sealed containers at room temperature) and its micro- and ultra-structures. The manner in which the gelator molecules are self-assembled into aggregates and the aggregate–aggregate interactions are especially interesting, and a variety of techniques have been used to elucidate the nature of gelator self-assemblies.

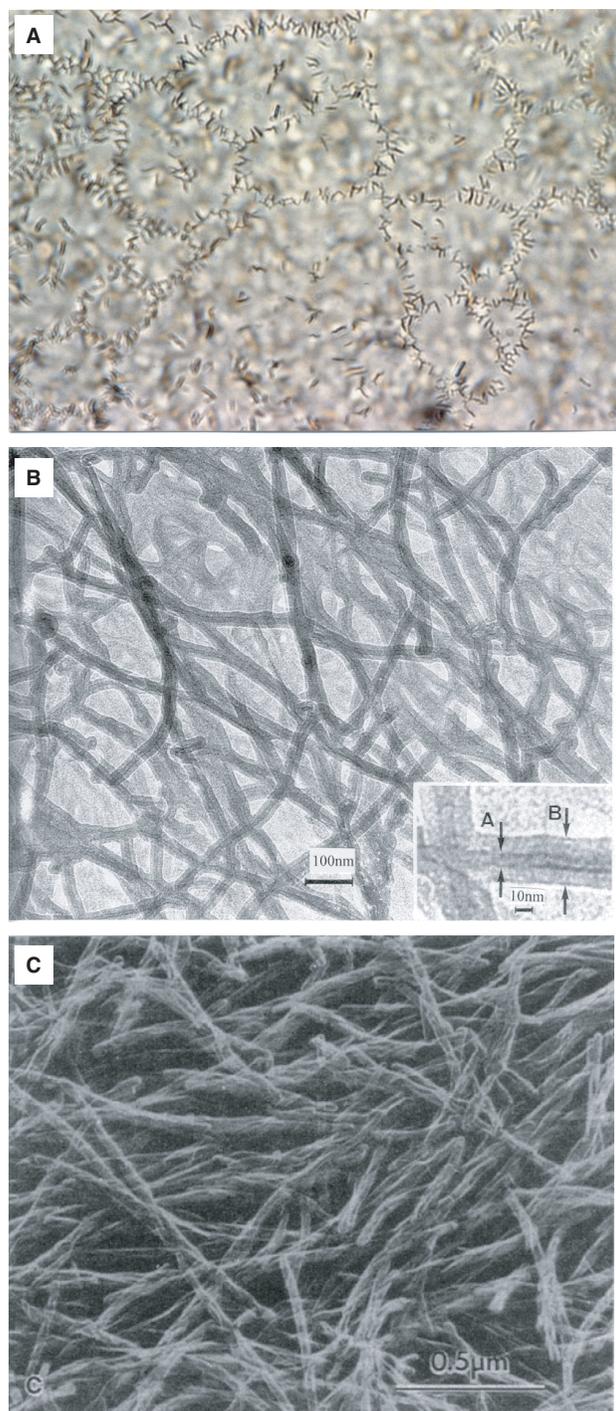


Figure 2. A. Microstructure of a sorbitan monostearate/isopropyl myristate organogel. B. Microstructure of SNO gels. WADE RH, TERECH P, HEWAT EA, RAMASSEUL R, VOLINO F: The network structure of a steroid cyclohexane physical gel. *J. Coll. Interface Sci.* (1986) **114**:442-451 [91]. Reproduced with permission from Elsevier (Copyright 2005). **C. Microstructure of CAB/octanol gel.** LIN Y, KACHAR B, WEISS RG: Novel family of gelators of organic fluids and the structure of their gels. *J. Am. Chem. Soc.* (1989) **111**:5542-5551 [18]. Reproduced, in part, with permission from American Chemical Society (Copyright 2005). CAB: Cholesterol 4-(2-anthryloxy)butanoate; SNO: d-Homosteroidal nitroxide.

1.3 Gelator self-assembly

A variety of gelator aggregates such as platelets, tubules, fibres, rods, worm-like chains, ribbons and fan-like structures have been reported. Aggregate thickness ranges from a fraction of a nanometre (e.g., when an aggregate consists of one gelator molecule per cross-section area) to microns; although, the diameter along the length of fibres seems to be fairly uniform, which may reflect unidimensional aggregate growth. The manner in which gelator molecules self-assemble and the nature of the gelator aggregate depends to a large extent on the gelator, whose component groups dictate the forces of interactions involved in gelator self-assembly. For example, molecules of the non-ionic surfactant sorbitan monostearate are thought to assemble into bilayers, which are then organised into tubules (Figure 3A). A bilayer arrangement is indicated from freeze-fracture microscopy and X-ray diffraction studies [14]. AOT/phenol gelator assemblies are thought to consist of stacks of phenol molecules, stabilised by π - π interactions between the aromatic electron clouds and by hydrogen bonding between the OH group of phenol and the sulfosuccinate head group of AOT [35,36] (Figure 3B). 12-Hydroxyoctadecanoic acid is thought to form fibrillar aggregates via extensive axial hydrogen bonding and dipolar interactions [40], as shown in Figure 3C.

Aggregation forces between gelator molecules thus include hydrogen bonding, dipole-dipole interactions, π -stacking, electron transfer, London dispersion forces, solvophobic effects, ionic interactions and so on, depending on the chemical structures of the gelators. It has been stated that the majority of gelators may be classified into hydrogen bond-based gelators; for example, those containing urea groups or non-hydrogen bond-based gelators (e.g., n-alkanes). A few gelators, such as those composed of cholesterol and sugar moieties [41], self assemble due to a combination of hydrogen and non-hydrogen bonding. Terech and Weiss have stated that aggregation strength depends on the intermolecular interaction energy, which is related to the number and type of intermolecular interactions per gelator molecule and the number of gelators per aggregate thickness [5]. The manner in which the gelator molecules are packed in aggregates must not be assumed to be the same as in the neat gelator solid, and the different packing and forces of interactions in gelator aggregates and in the neat solid are often reflected in the different melting points of the two.

The liquid phase of the gel plays a fundamental role in gelation and affects both macroscopic (e.g., opacity) and microscopic (e.g., aggregate size, shape, cross-sectional nature, helicity and gel network) properties of the gels. The fluid phase must provide the correct solubility/insolubility balance so that the gelator dissolves or is dispersed at high temperatures but comes out of solution (as aggregates) following cooling. A very good solvent will not be gelled as gelator-solvent interactions will stay strong following cooling of the sol phase. Solvent polarity has been shown to influence the shape of the

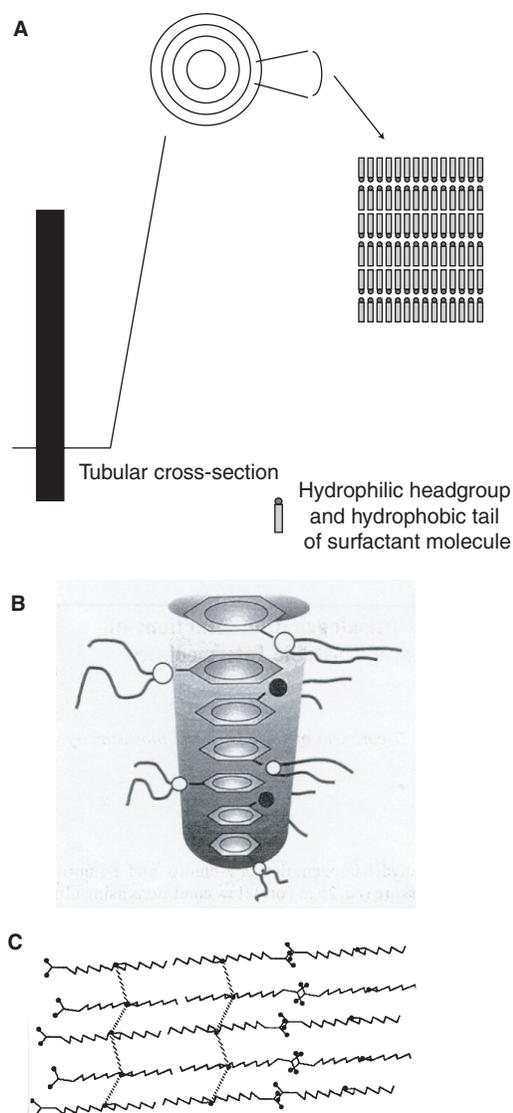


Figure 3. A. Schematic diagram shows the possible arrangement of bilayers within sorbitan monostearate tubules. B.

Schematic diagram shows the proposed stacking of phenol molecules and the position of AOT in AOT/phenol gels. TATA M, JOHN VT, WAGUESPACK YY, MCPHERSON GL: Microstructural characterization of novel phenolic organogels through high-resolution NMR-spectroscopy. *J. Phys. Chem.* (1994) **98**:3809-3817 [36]. Reprinted with permission from American Chemical Society (Copyright 2005). **C.** Schematic diagram shows the possible arrangement of 12-HOA molecules in the fibrillar aggregates and the axial hydrogen bonding. TERECH P: 12-D-Hydroxyoctadecanoic acid organogels: a small angle neutron scattering study. *J. Phys II France* (1992) **2**:2181-2195 [40]. Reprinted with permission from *J. Phys. II France*.

AOT: bis-(2-Ethylhexyl) sodium sulfosuccinate; 12-HOA: 12-Hydroxyoctadecanoic acid.

gelator aggregate; for example, D-DBS self-assemblies are rope-like and helical in the apolar p-xylene, much thinner in the moderately polar 1,4-dioxane, and fairly rigid and columnar in the highly polar dimethyl sulfoxide gels [42]. Molecular

shape of the solvent molecule can also have a profound effect on gelation; for example, steroidal nitroxide forms stable gels in *trans*-decalin and in cyclohexane but not in *cis*-decalin, methyl-cyclohexane and n-alkane [43]. The 'gellable' fluid phases, cyclohexane and *trans*-decalin, have the same rigid chair conformation as the gelator (Figure 4), which seems to favour gelation. The functional groups of the solvent also affect gel characteristics through specific solvent-gelator interactions, such as hydrogen bonding and dipole-dipole interactions. For example, gels of cholesteryl 4-(2-anthryloxy) butanoate (CAB) in 1-octanol and in n-alkanes melt at 63°C and at 43°C, respectively [18]. The higher melting point was thought to be due to the additional attractive forces provided by hydrogen bonding between 1-octanol and CAB in octanol gels. Hydrogen bonding between the OH groups of octanol and specific locations on CAB self-assemblies was also thought to be the reason for helicity of CAB fibres in 1-octanol but absence of such helicity in n-alkanes [18].

Other factors that influence gelator self-assembly includes the presence of additives, which may influence gelator solubility in the liquid [14] or may interrupt gelator-gelator interactions and thereby act as 'chain terminators' or 'chain-growth inhibitors' if they have a strong affinity for the gelator molecules [5]. Murdan *et al.* have previously reported that the inclusion of small amounts of polysorbate 20 increased the solubility of sorbitan monostearate in hexadecane and the stability of the resulting gel [14]. In addition, in the presence of polysorbate 20, 40, 60 or 80, sorbitan monostearate aggregates consist of star-shaped clusters of tubules (Figure 5). The clusters were not a result of preformed tubules joining at a central point but rather grew as an entity. The action of polysorbate 20 was solvent-specific; that is in short chain alkane ($C < 14$) gels, inclusion of polysorbate 20 decreased the solubility of the gelator in the liquid and the stability of the resulting gel.

The cooling rate of the sol phase also influences gelation; for example, alkane-in-alkane gels were prepared by cooling the sol phases under a stream of cold water, as slower cooling produced gels that were less stable [11]. The dimensions of the container in which gelation proceeds can also have an impact on the gel network. Furman and Weiss reported that if the size of the container was smaller than the mesh size of a particular gel network, gelation was either inhibited or a different type of gel network (mesh) was formed [44].

1.4 Organogels as drug delivery vehicles

One of the drivers of the growing research on organogelators and their gels is the range of potential industrial applications. This includes immobilisation of enzymes for biocatalysis, synthesis and transformation of toxic wastes, separation technology, temperature sensors, flatbed displays, recovery of oil spills and templates for the creation of inorganic structures [5,8,9]. Only a few organogels have been investigated for drug delivery despite the very large number of organogels under study. Reasons for this include the fact that most organogels are composed of pharmaceutically unacceptable (or untested)

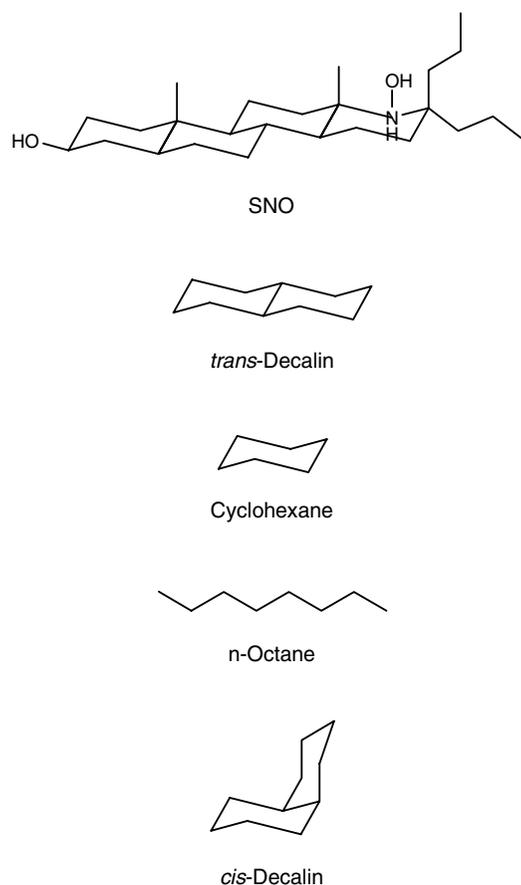


Figure 4. Chemical structures showing the rigid chair conformation of SNO (the gelator) and of cyclohexane and *trans*-decalin (the 'gellable' solvents). In contrast, the 'non-gellable' solvents, methyl cyclohexane and *cis*-decalin, do not have the same conformation as the gelator.

SNO: D-Homosteroidal nitroxide.

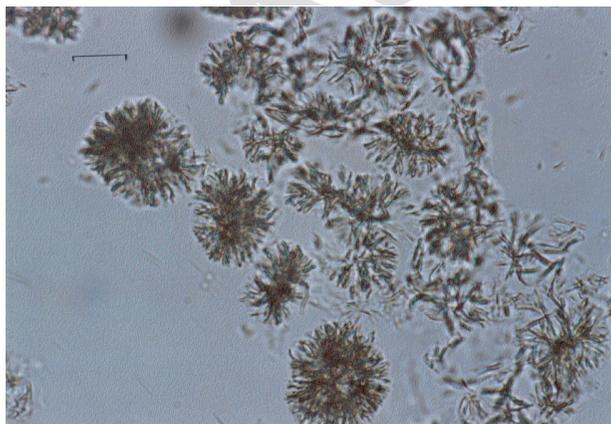


Figure 5. Sorbitan gel microstructure consists of clusters of tubules in the presence of small amounts of polysorbate 20.

gelators and organic solvents, and that most organogels are being investigated in chemistry or physics departments, where drug delivery may not be a focus of research. Organogels that have been studied for drug delivery include *in situ* forming organogels from L-alanine derivatives, Eudragit gels, lecithin gels, microemulsion-based gels (MBGs) and sorbitan monostearate gels. The latter are the only organogels that have been investigated for vaccine delivery. Pluronic lecithin organogels (PLOs) are not strictly speaking organogels but are included in this review as explained in Section 7. Organogels have mainly been investigated for transdermal drug delivery, although oral, rectal and parenteral routes have been studied to a smaller extent. Drugs may be incorporated into the gels during gel formation or may be mixed in preformed gels. Most of the drugs studied have been hydrophobic molecules, which are dissolved in the organic liquid phase. Hydrophilic entities (such as vaccines) have been dissolved in small volumes of an aqueous medium, which is then incorporated into the organogel. The different organogels are discussed in more detail below.

2. Sorbitan monostearate organogels and amphiphilic gels

2.1 Sorbitan monostearate organogels

Sorbitan monostearate (Span 60) and sorbitan monopalmitate (Span 40) have been found to gel a number of organic solvents at low concentrations [14]. Span 60 gels were found to be more stable than Span 40 gels and were investigated in greater depth. The thermoreversible gels are prepared by heating the gelator/liquid mixture in a water bath at 60°C (which results in dispersion of the gelator in the liquid medium) and cooling in dispersion of the gelator in the liquid medium) and cooling of the resulting suspension, following which the latter sets to an opaque, white, semisolid gel. Cooling results in reduced affinities between the solvent and the gelator molecules, which self-assemble into tubules. X-ray diffraction and freeze-fracture studies indicate that sorbitan monostearate molecules are arranged in inverted bilayers within the tubules, as shown in Figure 3A. The tubules form a three-dimensional network (e.g., in Figure 2A), which immobilises the liquid, and hence a gel is formed. For an organic liquid to be gelled by sorbitan monostearate, the liquid must provide the correct solubility (following heating) and insolubility (following cooling the sol phase) towards the gelator. Sorbitan monostearate gels alkanes ($C > 5$) such as hexane, cyclohexane, octane, *cis*- and *trans*-decalins, hexadecane, the alkene squalene, vegetable oils (e.g., corn oil, olive oil) and the long-chain synthetic esters, isopropyl myristate, ethyl oleate and ethyl myristate. The ungellable solvents include the more polar alkanols, ethanol, 2-propanol and butanol, and chloroform and dichloromethane, which dissolve sorbitan monostearate upon heating but from which the sorbitan monostearate precipitates out upon cooling. Benzene and toluene are very good solvents for sorbitan monostearate and cannot be gelled because, following cooling the sol phase, sorbitan monostearate remains dissolved in the solvent.

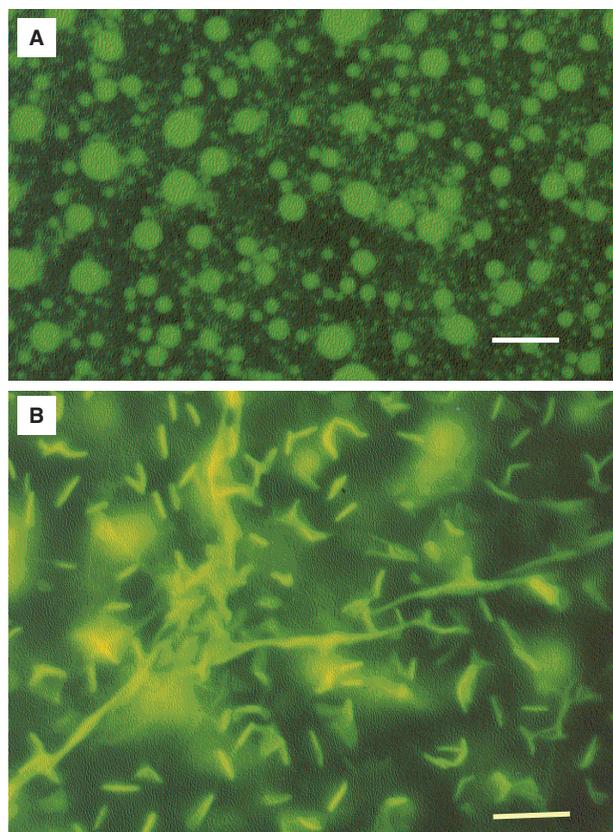


Figure 6. A. Light micrograph shows a conventional water-in-oil emulsion when the system temperature is high. Scale bar represents 50 μm . **B.** Light micrograph of a water-in-oil gel; the aqueous phase is accommodated within the gelator tubules. Scale bar represents 25 μm .

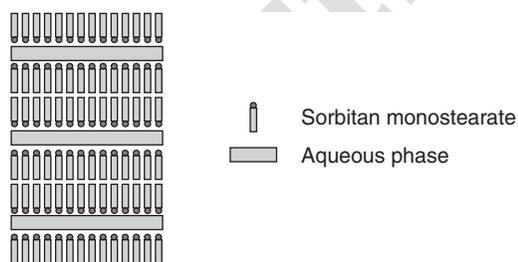


Figure 7. Schematic diagram shows the proposed accommodation of the aqueous phase within gelator bilayers in the gelled water-in-oil emulsion.

Sorbitan monostearate gels were investigated as delivery vehicles for hydrophilic vaccines [45]. To incorporate a hydrophilic molecule within the gel, an aqueous medium (containing the hydrophilic molecule) is added dropwise to a hot sol phase (e.g., 10% w/v sorbitan monostearate + 2% w/v polysorbate 20 in isopropyl myristate) while vortexing [46]. This produces a w/o emulsion (Figure 6A), which gels to an opaque thermoreversible semisolid following cooling. Light microscopy on the gel revealed that the aqueous phase

(containing a fluorescent dye) was located within the gelator aggregates (Figure 6B). As mentioned above, the gelator aggregates are thought to consist of bilayers of the surfactant. The bilayers comprise hydrophilic regions bound by the hydrophilic head groups of the surfactant molecules and it is thought that the aqueous phase is accommodated within the surfactant bilayers as schematically shown in Figure 7. X-ray diffraction studies, which showed an increased repeating unit width (from 5.9 to 6.9 nm) following inclusion of water in a sorbitan monostearate gel also suggests that the aqueous phase is located within the bilayers. In addition, freeze-fracture experiments showed the presence of layers in a w/o gel.

It was hypothesised that a w/o gel containing a hydrophilic vaccine may act as a depot for the vaccine following intramuscular administration *in vivo*, as the organic phase presents barriers to the diffusion of the hydrophilic vaccine. To investigate the possibility of a depot effect, a w/o gel containing a radiolabelled (^{125}I) model antigen (bovine serum albumin [BSA]) was intramuscularly administered in the right hind leg of 18 mice and the radioactivity remaining at the site of injection with time was monitored. At different times post-injection three mice were killed, the injected leg was amputated, and the radioactivity remaining in the leg was measured using a γ -counter. The count obtained was expressed as a percentage of the initial total radioactivity at time 0. Control mice received intramuscular injections of an aqueous solution of BSA. The percentage radioactivity remaining at the site of injection, with respect to time, is shown in Figure 8. BSA was rapidly cleared following administration of an aqueous solution but much less so from the w/o gel. The organic medium in the gel delayed the absorption of BSA into the systemic circulation and clearance from the injection site. The depot effect was of a short duration, however. It was thought that following gel administration *in vivo*, the local interstitial fluid penetrated into the organogel via the interconnected tubular network. This would result in the breakdown of the gel mass into smaller fragments, from which the release of BSA could occur relatively fast. This was inferred from *in vitro* studies on the interactions between the gel and an aqueous phase [47]. The study showed that sorbitan monostearate organogels could not be used as long-term sustained release implants, but could have applications where a short-term depot was required.

Multi-compartment sorbitan monostearate organogels were prepared when an aqueous vesicle suspension was incorporated into organogels [48]. The gels were prepared by adding a hot aqueous vesicle (niosome) suspension (v/w) dropwise to an organosol at 60°C while vortexing. A vesicle-in-water-in-oil (v/w/o) emulsion (Figure 9A) was produced, which on cooling set to a semisolid, thermoreversible v/w/o gel. Light microscopy revealed that the aqueous niosome suspension was dispersed within the fibrillar aggregates (Figure 9B). Such v/w/o gels, in which haemagglutinin (HA) antigen was entrapped within the niosomes, were investigated as immunoadjuvants

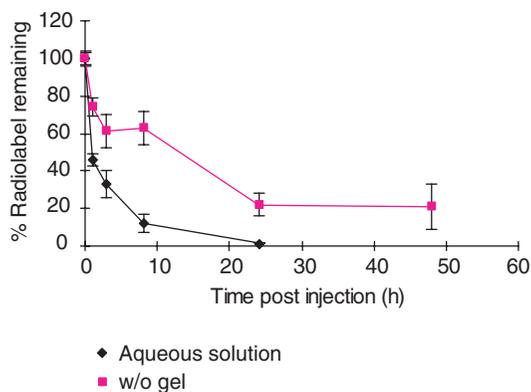


Figure 8. The percentage radioactivity remaining at the site of injection, with respect to time, following intramuscular administration of an aqueous solution and a w/o gel containing radiolabelled BSA. Error bars are standard deviations. BSA: Bovine serum albumin; w/o: Water-in-oil.

[49]. It was thought that a combination of niosomes and w/o emulsion, both of which show immunoadjuvant properties, would produce a stronger adjuvant effect. Indeed the v/w/o gel enhanced the primary and secondary antibody titres to 0.7 μg HA in mice, compared with a vesicle suspension and an aqueous HA suspension. Interestingly, a w/o gel containing the same amount of HA enhanced antibody titres to the same extent as the v/w/o gel, thus showing no benefit of including vesicles. The lack of a beneficial effect was thought to be due to the low vesicular component in the gel; it was suggested that the adjuvant effect of the w/o gel was so large that a small enhancement by the vesicular component was unnoticed. At lower HA concentration (0.1 μg), the w/o gel produced greater IgG antibody responses compared with the v/w/o gel. The deleterious effect of including niosomes on the immune responses was thought to be due to the low antigen content of the vesicles; a low antigen content per vesicles had previously been shown to curtail vesicular adjuvancy [50,51].

2.2 Sorbitan monostearate amphiphilogels

The non-ionic surfactants, sorbitan monostearate and sorbitan monopalmitate, were also found to gel other non-ionic surfactants such as liquid sorbitan esters (e.g., sorbitan monooleate and polysorbates). Based on the amphiphilic nature of the liquid component of these gels, the latter were termed 'amphiphilogels' [52]. The amphiphilogels can be hydrophilic when the liquid phase is a hydrophilic polysorbate or hydrophobic when the liquid is a hydrophobic sorbitan ester. These gels are prepared in the same way as sorbitan ester organogels, have similar microstructures and are stable for ≥ 2 years when kept in sealed containers at room temperature [34,53]. The amphiphilogels can solubilise certain poorly water-soluble drugs such as cyclosporin, ibuprofen, aspirin and paracetamol. Drug solubilisation in the gel alters the Tg (it can increase or decrease, depending on the nature of the drug) and the gel microstructure [53]. The amphiphilogels

were investigated as oral vehicles for cyclosporin. *In vivo* experiments in mice [54] and dogs [55] that were orally dosed with cyclosporin-containing gels showed high oral absorption; maximum concentration (C_{max}) and area under curve (0–24h; AUC_{24}) being similar to those achieved with the commercial preparation Neoral[®] in dogs [55], but higher in mice [54]. High drug absorption was thought to be because the drug did not precipitate out following oral administration but stayed in a solubilised form when the gel interacted with aqueous gastric fluids.

Water-soluble active agents; for example proteins and antigens can also be incorporated into hydrophilic amphiphilogels. This is done by dissolving the active agent in an aqueous phase, adding the latter to a gel and heating the mixture to 60°C, and vortexing to form an isotropic solution, and cooling the resulting solution at room temperature to allow gelation [53]. The addition of an aqueous phase into the amphiphilogels reduces gel Tg and alters the gel microstructure and its rheology. Protein stability seems to be maintained following incorporation into the gel, and amphiphilogels containing a model antigen, ovalbumin, were studied as vehicles for skin vaccination [53]. Topical application of ovalbumin in gels did not result in the generation of ovalbumin-specific antibodies. This shows that vaccine permeation into the skin did not occur to a sufficient extent. This may be related to the fact that the gels did not disrupt the stratum corneum sufficiently [56] to allow permeation of ovalbumin. In fact, the gels were found to cause almost no irritation to the skin of mice and of men when applied twice a day for 5 consecutive days [56].

3. *In situ* formation of an organogel of L-alanine derivative

N-lauroyl-L-alanine methyl ester (LAM) was found to gel the pharmaceutically acceptable organic solvents, soybean oil and medium-chain triglycerides [57]. Normally, the system exists in the gel state at room temperature. However, the addition of ethanol to a gelator/solvent solution inhibits gelation because the ethanol disrupts the formation of hydrogen bonds (essential for gelator self-assembly into aggregates) between the gelator molecules. This means that a solution of LAM in an organic solvent can remain in the sol phase at room temperature when some ethanol is added to the mixture. When such a sol phase (20% LAM + 14% ethanol in soybean oil) was placed in phosphate buffered saline at 37°C it turned into a opaque gel within 2 min as the hydrophilic ethanol diffused away into the aqueous buffer, and as gelator-gelator hydrogen bonds were formed. Thus, theoretically, such a LAM/ethanol/soybean oil solution could form gels *in situ* following its subcutaneous injection, due to ethanol diffusion away from the formulation, into the surrounding tissues; *in situ* gel formation in rats was indeed investigated [57]. The main advantage of *in situ* forming gels is their injectability at room temperature. Once a drug-containing gel is formed *in situ*, it could act as a sustained-release implant.

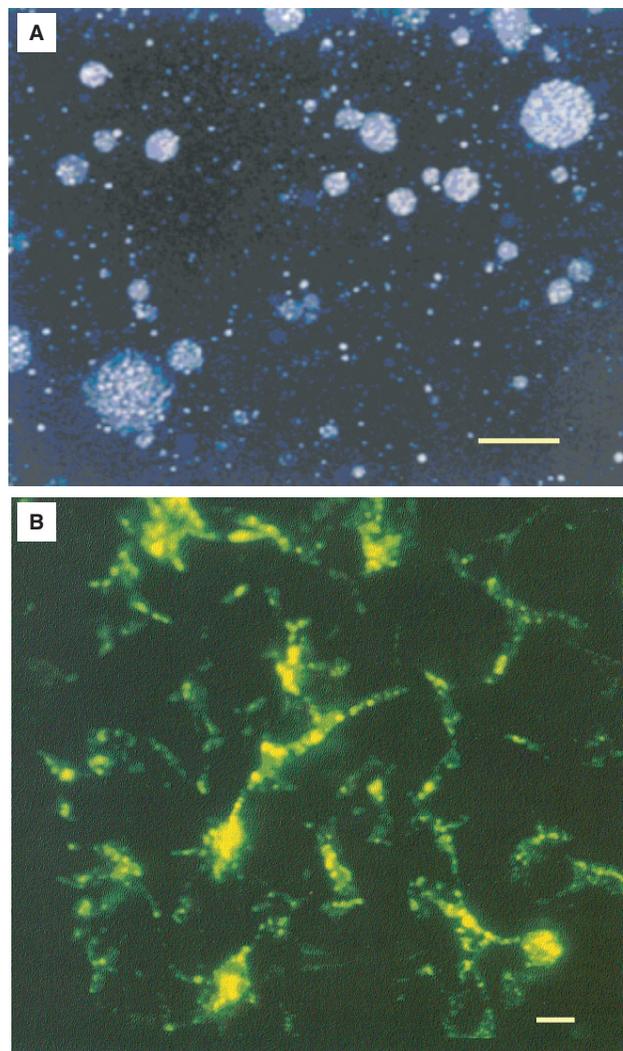


Figure 9. A. Light micrograph of a hot vesicle-in-water-in-oil emulsion; vesicles are present within water droplets. Scale bar represents 10 µm. **B. Light micrograph of a vesicle-in-water-in-oil gel; vesicles are present within fibrils.** Scale bar represents 10 µm.

For the *in vivo* studies, the injectable sol phase was produced by dissolving LAM in ethanol, followed by the addition of soybean oil, and stirring and heating the mixture until a homogeneous solution was obtained. The latter liquid (containing 30% LAM w/v and 18% ethanol v/v in soybean oil) was subcutaneously injected into the dorsal area of a group of rats. Following administration, gel formation into a bean-shaped implant was observed at the site of injection after 2 h. Dissection of sacrificed experimental animals at 24 h or 9 days post-injection revealed that the gel's integrity did not change with time. Excision of the implant did not affect the latter's integrity either. Further *in vivo* studies to determine the *in situ* formation of drug-containing gels, the drug release profiles from these gel implants, their lifetime and any adverse effects must be conducted to fully assess these novel gels; some of these studies are currently underway [57].

4. Eudragit organogels

Eudragit organogels are different from the organogels described in the introduction section as they are really mixtures of Eudragit (L or S) and polyhydric alcohols, such as glycerol, propylene glycol and liquid polyethylene glycol, containing high concentrations (30 or 40% w/w) of Eudragit. Drug-containing gels were prepared by dissolving the drug (salicylic acid, sodium salicylate, procain or ketoprofen) in propylene glycol, pouring the resulting solution into Eudragit powder (contained in a mortar), and immediately mixing with a pestle for 1 min [58,59]. The authors did not describe the gel appearance or microstructures, but measured gel consistency and spreading using a penetrometer and a spreadmeter [58]. Gel viscosity was found to increase with increasing concentrations of Eudragit and to decrease with increasing drug content. The inclusion of the drug procaine was also found to reduce gel rigidity, which was thought to be due to the influence of the drug molecules on the intermolecular forces (e.g., hydrogen bonds) between Eudragit and propylene glycol. The authors suggested that drug content in Eudragit organogels be kept low (e.g., 1.25% w/w) to maintain gel rigidity and stability. The release of model drugs salicylic acid, sodium salicylate and ketoprofen from Eudragit L and S organogels was investigated *in vitro* by the rotation disk method [59]. Interestingly, the mechanism of salicylic acid release from Eudragit L and S organogels into a phosphate buffer were totally different. Release was due to surface erosion of the Eudragit L organogel but to diffusion through the Eudragit S gel matrix. Drug release from Eudragit S organogel thus increased with increasing temperature and agitation rate of the release medium.

Eudragit L organogels were evaluated as rectal sustained-release preparations in rabbits [58]. Gels containing salicylic acid or sodium salicylate or ketoprofen were administered rectally to male rabbits using a specially constructed syringe. Witepsol H-15 suppositories containing the same drugs were used as controls. The plasma concentration profiles of the gel and of the control were found to be different; slower drug absorption was obtained from Eudragit gels. However, no statistical difference was found between the area under the curves of Witepsol H-15 suppositories and Eudragit L organogels with respect to the absorption of the three drugs. Addition of an absorption enhancer such as linolic acid or oleic acid at 10% w/w in the gels resulted in increased drug absorption, and Eudragit L organogel containing an absorption enhancer was suggested as a possible sustained-release suppository base [58].

5. Microemulsion-based gels

5.1 Gel formation

Microemulsion-based gels (MBGs) are also different from most organogels in that the gelator, gelatin, is a hydrophilic polymer, which gels water. MBGs were initially prepared by dissolving solid gelatin in a hot water-in-oil microemulsion (which was composed of water, AOT and isooctane)

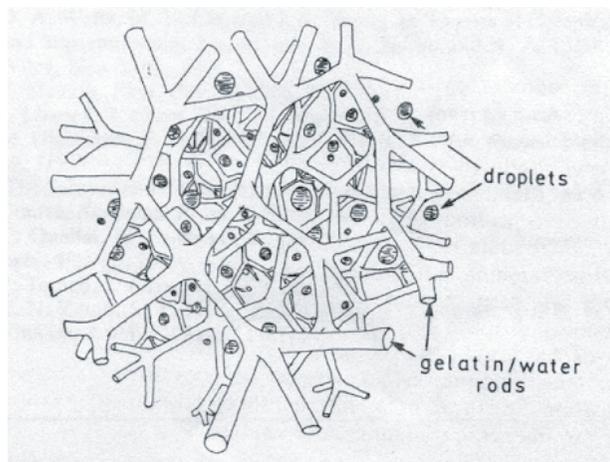


Figure 10. A proposed structure of MBG; an extensive network of rigid rods of water and gelatin coexisting with microemulsion water droplets. ATKINSON PJ, GRIMSON MJ, HEENAN RK, HOWE AM, ROBINSON BH: Structure of microemulsion-based organo-gels. *J. Chem. Soc. Chem. Commun.* (1989) **23**:1807-1809 [60]. Reproduced by permission of The Royal Society of Chemistry.

followed by cooling [39]. The researchers expected that the gelatin would dissolve in the water droplets of the w/o microemulsion and that cooling of the system would result in gelation of the water droplets, which would lead to clouding of the system and possibly phase separation. To their surprise, the whole microemulsion gelled to a transparent semisolid with a high viscosity and a high electro-conductivity. A w/o microemulsion comprising 80 – 90% oil phase (iso-octane + AOT) had been gelled by a relatively small amount (7 – 11% w/v) of gelatin: a hydrophilic polymer that would be present mainly in the water phase of the system. Such MBGs have also been prepared by the addition of an aqueous gelatin solution to a micellar solution of AOT in an organic solvent [60]. The T_g of the thermoreversible gel, measured by differential scanning calorimetry, was found to be in the region of 34 – 38°C, which is close to the transition temperature of gelatin hydrogels [61]. MBG microstructure is thought to consist of an extensive network of rigid rods of water and gelatin (surrounded by a shell of AOT surfactants) coexisting with microemulsion water droplets [60-62] as shown in Figure 10, although other similar structures have also been proposed.

5.2 Microemulsion-based gels in drug delivery

One of the first applications of MBGs was the entrapment of enzymes, especially lipases, for esterification and catalysis [63]. For drug delivery applications, MBGs were formulated with pharmaceutically acceptable oil (e.g., isopropyl myristate) and by replacing $\leq 85\%$ of the anionic AOT with the more acceptable non-ionic surfactants such as Tween 21, 81 and 85 [64,65]. The resulting MBGs had an appropriate viscosity for

topical application to the skin, were electro-conducting and were, therefore, investigated as vehicles for iontophoretic transdermal drug delivery [65]. The model water-soluble drug (sodium salicylate) was entrapped within MBG by the addition of solid gelatin to a w/o microemulsion containing the drug, heated with stirring until the gelatin dissolved, and allowed to cool to room temperature. It is thought that the drug was present in the water compartments of the gel; that is within the rigid rods as well as the water droplets. However, it not known whether there was an exchange of drug molecules between the droplets and the rods. *In vitro* studies using adapted Franz diffusion cells were conducted to measure drug flux through split-thickness porcine skin. Under passive conditions, the drug flux from an aqueous drug solution (the control formulation) and from a drug-loaded MBG were comparable, and were essentially first order with respect to the donor concentration. The advantage of the gel over the aqueous drug solution was said to be its higher viscosity, making it suitable for topical application, and its resistance to microbial contamination due to the large apolar oil component. When an electrical current was applied to the MBG or to the control aqueous drug solution, the drug flux through the porcine skin was enhanced as iontophoresis of the drug occurred. Drug flux from the aqueous solution was, however, greater than that from the MBG. This was presumably due to the fact that all the drug molecules in the aqueous solution were available for permeation into the skin, whereas part of the drug entrapped within the MBG was present in the dispersed aqueous droplets and may not have been influenced by the applied electrical current. As expected, increasing current density from 0.179 to 0.385 mA/cm² resulted in increased drug flux and reduced the lag time for drug penetration. Lag time was also inversely proportional to the drug concentration in the MBG. The latter has shown promise as a vehicle for iontophoretic transdermal drug delivery in these *in vitro* studies. *In vivo* studies have yet to be conducted to investigate iontophoretic transdermal drug absorption from MBGs.

Agrawal *et al.* investigated MBGs, as well as lecithin organogels (described in the next section), as transdermal vehicles for piroxicam [66]. They reported that MBGs did not cause any sensitisation when applied to the shaved back of rabbits for a period of 3 days. The permeation of the drug from MBG *in vitro* and *in vivo* was compared with that from lecithin gel and from a marketed formulation, and is described in the next section.

6. Lecithin organogels

6.1 Gel formation

A lecithin organogel is formed when small amounts of water or other polar substances, such as glycerol, ethylene glycol or formamide, are added to a non-aqueous solution of lecithin [37,38,67,68]. The molar ratio of water to lecithin ($w_0 = [H_2O]/[lecithin]$) is typically 2:10 and depends on the nature of the organic solvent. Excess water leads to destabilisation of the gel

and phase separation. A wide range of non-aqueous solvents such as linear, branched and cyclic alkanes, ethers and esters, fatty acids and amines containing lecithin have been gelled following the addition of small amounts of water. Gel formation is thought to be due to changes in the structure of the lecithin micelles in the non-aqueous medium: before the addition of water (or glycerol, ethylene glycol or formamide), the surface active lecithin molecules are present as spherical reverse micelles in the non-aqueous medium. The addition of water is thought to cause uniaxial growth of the micelles into giant cylindrical micelles, which overlap and entangle, and form a three-dimensional network [37]; an increase in viscosity and gel formation are the result. This theory is widely accepted, but some controversy exists [69,70]. Conversion of the spherical micelles into giant cylindrical ones is thought to happen when the added molecules of water (or formamide, ethylene glycol or glycerol) form hydrogen bonded 'bridges' between the phosphate head groups of neighbouring lecithin molecules, allowing their assembly into tubular aggregates [38].

6.2 Drug incorporation into lecithin organogels

Lecithin organogels have been used as carriers for hydrophilic and hydrophobic drug molecules. Hydrophobic drugs are dissolved in the oil phase (lecithin + organic solvent) [71], whereas hydrophilic molecules are dissolved in water, which is then added to an organic solution of lecithin to induce gelation [72]. Concentration of hydrophilic drug in these gels thus depends on the amount of water that produces a good gel. This, in turn, depends on the organic solvent used, for example, lecithin solutions of long-chain fatty acid esters, such as isopropyl palmitate are gelled by very small amounts of water, whereas lecithin solutions of cyclo-octane can incorporate much larger amounts of water. To increase the amount of water (and hence the amount of hydrophilic drug) incorporated in the gels, Nastruzzi *et al.* used mixtures of organic solvents, for example, isopropyl myristate and short-chain esters, such as ethyl or propyl acetate, the latter at 10 – 20% [72].

Drug incorporation into lecithin organogels has effects on the drug as well as on the gels. The solubility of certain drugs, such as broxaterol and nifedipine, was enhanced compared with solubility in the neat solvent [71]. For example, the solubility of broxaterol in isopropyl palmitate and in an isopropyl palmitate/lecithin organogel was found to be 11 and 75 mg/ml, respectively. The drug is expected to be solubilised within lecithin micelles. Drug incorporation has been reported to reduce gel viscosity, sometimes to a small extent only [72] but at other times the gel can be destroyed; for example, by the addition of high concentrations of indomethacin or diclofenac [73]. Care must be taken, therefore, when lecithin gels are used as drug carriers.

6.3 Lecithin gels as transdermal drug delivery vehicles

Isopropyl palmitate/lecithin organogels were tested as matrices for transdermal drug delivery [71]. Isopropyl palmitate was

used as the oil component because of its pharmaceutical acceptability. Drug-containing gels were prepared by dissolving lecithin and the model drug (scopolamine or broxaterol) in the organic solvent, followed by the addition of water to induce gelation. The permeation of drug solubilised in the gels through excised human skin was tested *in vitro* using Franz diffusion cells. The transport rate of scopolamine from the lecithin gel into the receptor phase was ~ 10 times higher than the transport rate from an aqueous scopolamine solution. Interestingly, the transport rates of the drug (scopolamine or broxaterol) from lecithin/isopropyl palmitate gel and from a lecithin solution (the system prior to the addition of water [prior to gelation]) were similar. This shows that gelation did not influence the rate of drug transport through the skin. Enhanced drug permeation through the skin was assigned to the effects of lecithin on the skin. Lecithin (from the organogel or the solution prior to gelation) was thought to penetrate into the skin, interact and disorganise the lipid layers of the stratum corneum. This would result in increased drug movement into and through the skin. Lecithin has previously been shown to act as a skin penetration enhancer when present at a concentration of 1% [74].

Lecithin/isopropyl myristate organogels have also been tested as transdermal delivery vehicles for piroxicam to reduce the drug's adverse effects and to avoid its first pass metabolism when administered orally [66]. *In vitro* investigations in diffusion cells showed that 40% of the drug present in the gel had permeated through excised abdominal rat skin after 8 h. The *in vivo* drug permeation was assessed by measuring the drug's anti-inflammatory effect vis-a-vis the inhibition of carageenan-induced rat paw oedema. Drug-loaded lecithin organogel was applied to the shaved abdominal skin of albino rats and carageenan suspension was injected into the right hind paw of the rats after 1 h. The paw volume was measured for treated and control rats. The latter received applications of lecithin organogels without drug. Application of the drug-loaded lecithin organogels was found to significantly inhibit oedema and changes in the hind paw volume compared with the control formulation, thus indicating that piroxicam had permeated through the skin following topical application, had been absorbed into the systemic circulation and had acted away from the application site. As mentioned in Section 5, the researchers also investigated microemulsion-based organogel as a vehicle for piroxicam. In this rare example of a study, in which two different organogels were compared, lecithin gel was found to be superior to the MBG when the *in vitro* permeation of piroxicam and the *in vivo* inhibition of carageenan-induced rat paw oedema were compared. Both the lecithin gel and the MBG were, however, superior to the marketed product at inhibiting rat paw oedema.

Lecithin/isopropyl palmitate gels have also been reported to enable the permeation of a water-soluble anticancer agent, the bromo derivative of tetra-*p*-amidinophenoxy neo-pentane (TAPP-Br), through the skin and act locally on a subcutaneous tumour [72]. In these studies, a tumour mass was generated in

mice following the subcutaneous injection of tumour cells. At days 6, 8 and 10, lecithin gel containing TAPP-Br was applied on the skin, either directly surrounding the tumour lesion or away from the tumour site. Control tumour-bearing mice were treated with empty lecithin gels (i.e., gels containing no drug) applied on the skin surrounding the tumour lesion. The tumour growth was followed with time. The researchers found that tumour growth was arrested only when drug-containing lecithin gel was applied onto the skin directly around the tumour site. This indicates permeation of TAPP-Br through the skin and its action on the subcutaneous tumour. Permeation of TAPP-Br through the skin is impressive given its large molecular weight and its hydrophilicity, and shows that lecithin gel must have disrupted the stratum corneum of the skin to some extent. Absence of tumour growth arrest when the drug-containing lecithin gel was topically applied away from the tumour site suggests that the drug was not absorbed into the systemic circulation; or, it is possible that the drug was absorbed into the systemic circulation but was present at insufficient concentrations to have any effect on tumour growth. Absorption of the anticancer agent into the skin shows that lecithin gels could be used as vehicles for the treatment of skin tumours.

In the studies described above, lecithin was thought to be the agent that enhanced the skin permeation of the drug molecules [66,71]. The role of lecithin as the permeation enhancer in a lecithin/isopropyl palmitate organogel has, however, been questioned by Dreher *et al.* [73], who investigated the interactions between lecithin gels and human stratum corneum using Fourier transform infrared spectroscopy, differential scanning calorimetry and low-temperature scanning electron microscopy. FTIR spectra of stratum corneum exposed to lecithin/isopropyl palmitate gel or to neat isopropyl palmitate (IPP) for 5 days showed absorption peaks related to isopropyl palmitate but not to lecithin. IPP had permeated into the stratum corneum, whereas lecithin had not. In addition, permeation of IPP into the stratum corneum, from the gel and from neat IPP occurred to the same extent. This shows that lecithin did not enhance IPP permeation into the stratum corneum. Differential scanning calorimetry on the stratum corneum exposed to lecithin gel or to neat isopropyl palmitate showed reductions in two of the four endothermic peaks of the stratum corneum. Such reductions have been assigned to disruptions of the lipid bilayers in the stratum corneum, and have previously been reported for certain skin permeation enhancers, such as azone, and for isopropyl myristate (which is closely related to isopropyl palmitate). Based on these studies, Dreher *et al.* seem to favour the idea that isopropyl palmitate (and not lecithin) was the transdermal enhancing agent in lecithin/IPP gels [73].

6.4 Tolerability/irritation potential of lecithin gels

Transdermal enhancers act by causing a certain amount of damage to the skin, which allows drug molecules to penetrate into the skin. The damage caused must be small and reversible for a drug formulation to be acceptable to patients, and,

therefore, the irritation potential of lecithin organogels applied to the skin has been investigated *in vitro*, in animals and in man. Willimann *et al.* conducted preliminary histological studies on skin samples that had been used in their *in vitro* permeation studies for 3 days and showed that the stratum corneum of the skin exposed to lecithin gels were intact [71]. Agrawal *et al.* applied piroxicam-loaded lecithin/isopropyl myristate gels to the shaved backs of rabbits and found that the gels did not produce any sensitisation during a 3-day observation period [66]. Dreher *et al.* investigated the acute (48 h patch test) and cumulative (21-day repeated insult patch test) irritation potential of lecithin gels in human volunteers and showed that the gels caused little irritation [75]. In the latter study, 2 of the 151 volunteers taking part in the acute test suffered from slight erythema at the application site. In the cumulative irritation test, significant irritation was observed in 8 of the 16 volunteers following 13 days of continuous gel exposure to the same skin site. In practice, the site of gel application would be rotated on consecutive days; the cumulative insult test was conducted to assess the irritation in case the gel was misused and applied to the same skin site repeatedly. These investigations increase the likelihood that lecithin gels containing a biocompatible liquid will be used as transdermal or topical drug delivery vehicles.

7. Pluronic lecithin organogels

7.1 Pluronic lecithin organogel history

The story of PLO, a gel derived from lecithin organogels, is fascinating. An opaque, yellow gel, PLO is composed of isopropyl palmitate, soy lecithin, water and the hydrophilic polymer, Pluronic F127. The difference between PLO and its precursor, lecithin gels, is the presence of Pluronic F127 (a hydrophilic polymer that gels water) and the greater amount of water compared with the oil. Thus, PLO is not really an organogel but is briefly reviewed in this paper because it may be thought of as an 'organogel' due to its name.

PLO was developed by a compounding pharmacist in the US in the early 1990s as a topical vehicle [76]. Pluronic F127 was added to the original lecithin organogel in order to stabilise the gel formulation. The gel's physicochemical properties have not been investigated. However, collaborations between local physicians, their patients and the inventor pharmacist led to the incorporation of many different drugs, such as non-steroidal anti-inflammatories, haloperidol, prochlorperazine and secretin for patient use and to anecdotal evidence of its efficacy as a transdermal drug delivery vehicle. Many more drugs have since been incorporated within PLO, and the related references may be found at the *International Journal of Pharmaceutical Compounding* website [101]. Mainly used as a topical or transdermal drug carrier, for example, for hormones [77,78], PLO has also been investigated/proposed as a vehicle to the oral cavity and mucosa [79-81]. Anecdotal evidence of its efficacy has also led to its use by veterinarians for transdermal drug application to pets, especially cats.

7.2 *In vivo* studies in cats

Only a handful of systematic studies have been conducted to probe the efficacy of the gel as a transdermal delivery vehicle. *In vivo* studies in healthy cats showed that topical application of drug (methimazole [82], fluoxetine [83], dexamethasone [84], amitriptyline and buspirone [85]) incorporated into PLO gel did not result in significant drug absorption into the systemic circulation, and plasma drug concentrations were either very low or undetectable following a single application of drug-containing PLO. Consequently, the authors advised caution regarding the substitution of oral medications by drug-containing PLO gels. In these studies, however, drug concentrations in the blood was measured following a single topical application. This does not reflect the use of PLO gel by pet owners in practice, where the gel is applied repeatedly and possibly to the same skin site in cats (inner ear). A retrospective study where methimazole-in-PLO was chronically administered to cats suffering from hyperthyroidism showed the resolution of many clinical symptoms (evaluated by veterinarians) and a reduction in total thyroxine levels [87,88]. The latter results and the anecdotal evidence of PLO efficacy as a transdermal drug delivery may, therefore, have arisen due to chronic application of the drug-in-PLO, probably to the same site, which could have resulted in irritation of the skin and enhanced drug absorption through the breached skin barrier. Substantial skin irritation after the application of PLO for several days has previously been reported [83].

7.3 *In vivo* studies in man

The limited *in vivo* studies in human patients suggest that PLO may be beneficial as a delivery vehicle for local action [88,89]. In these studies, diclofenac-in-PLO was applied three times daily for 2 weeks [88] and for 1 week [89] to the affected site: in the treatment of osteoarthritis of the knee and of lateral epicondylitis, respectively. Following the application of PLO, patients experienced less pain [88,89] and increased wrist extension strength [89]. Drug levels in the blood were not, however, measured and drug absorption into the systemic circulation cannot be assumed. In a third study, the efficacy of PLO as a transdermal delivery vehicle for ondansetron following a single application, was evaluated in 12 healthy human volunteers [90]. PLO gel was reported to be a good topical vehicle for ondansetron. However, no control formulations were used, so the benefit of PLO over a simple ondansetron solution cannot be ascertained.

Further systematic *in vivo* studies, in cats and in man, must be conducted, where the dosing regimen reflects the chronic PLO application in practice, drug concentrations in the blood are measured, and disease progression/regression is monitored.

8. Expert opinion and conclusions

In the last 10 years there has been an explosive growth in research on organogels and on publications related to organogels. Most of the latter report the discovery and/or syn-

thesis of new organogelators, investigations into the chemical groups necessary for the molecule to be an organogelator, the properties of their gels including the gel microstructures, and the manner in which the gelator molecules could be arranged in the gelator aggregates. Research into the applications of these gels is still in its infancy despite great excitement about their potential industrial uses. As far as drug delivery is concerned, the absence of an aqueous phase is beneficial as the non-aqueous medium is less likely to support microbial growth. The non-aqueous medium of organogels also indicates their potential suitability as carriers for oil-soluble drugs, whereas their soft, semisolid consistencies point to their use as vehicles for application to the skin. However, only a few organogels have been investigated for drug delivery, mainly due to the fact that the components of most organogels are not pharmaceutically acceptable. Thus, before the organogels can be studied as a drug carrier, they must be reformulated using pharmaceutically acceptable components. Drug incorporation into the gels is known to alter the gel properties, such as viscosity, and, in some cases, drug incorporation even destroys the gel. Care must be taken, therefore, when drugs are dissolved or suspended in organogels and the drug-containing formulations must be thoroughly characterised. Currently, literature on the influence of drug incorporation on the physicochemical properties of organogels is limited.

Of all the organogels studied, MBGs seem to be the most investigated for their application as a matrix where enzymes can be immobilised for biocatalysis of reactions. In drug delivery, the potential of MBGs has not been fully explored. Only a few publications exist on MBGs as drug delivery vehicles despite much work on the formulation of a pharmaceutically acceptable MBG. Lecithin gels have received more attention as transdermal drug delivery vehicles, presumably due to the presence of lecithin: a known skin permeation enhancer. The promise shown by lecithin gels as a transdermal delivery vehicle has resulted in its adoption and adaptation into PLO (which is not an organogel despite the terminology). PLO is currently the vehicle of choice of US compounding pharmacists and veterinarians for the delivery of drugs by the topical route, despite the lack of any hard, scientific evidence of PLO efficacy as a transdermal drug carrier.

Apart from the topical/transdermal route, organogels have been investigated for oral, rectal and parenteral applications. Sorbitan monostearate organogels and amphiphilogels have shown promise as parenteral vaccine adjuvants and as oral vehicles for poorly water-soluble drugs, respectively. Given that many drugs suffer from poor water solubility, which often leads to low bioavailability, the ability of sorbitan monostearate amphiphilogels to solubilise such drugs to increase bioavailability should be investigated further. The potential of amphiphilogels to enhance the transdermal delivery of small drug molecules has not yet been investigated. This gap should be filled as one of the concerns of the amphiphilogels, their skin irritancy due to their composition of 100% surfactant, has been addressed and the gels were

found to have a low irritancy when applied twice a day for 5 consecutive days.

Eudragit organogels, different from 'classical' organogels in their large, polymeric 'gelator', the need for a high gelator concentration and the fact that they are mixtures of gelator and solvent, were studied > 10 years ago for rectal delivery. Bioavailability of the drug from these gels was not higher than from the control formulation (Witepsol), and it seems that research into Eudragit organogels for rectal delivery has been superseded by research into other, more promising formulations. More recently, organogels that form *in situ*, following the injection of a sol phase have been reported. *In situ* forming implants are advantageous over conventional implants in that they do not require surgical incision but can be administered by injection. The alanine derivative gels will be interesting as sustained-release depot preparations.

As is common in drug delivery research, the different organogels have not been investigated in the same study, so it is not possible to compare them, except for one investigation in which MBGs and lecithin gels were studied as transdermal vehicles for piroxicam. In that investigation, MBGs were found to be inferior to lecithin gels. This is the result of only one study, however, and one cannot draw too many conclusions. In transdermal drug delivery, lecithin gels have the advantage of containing lecithin, a known skin permeation enhancer. An investigation comparing the different organogels would be of interest to researchers and companies seeking to develop a drug-in-organogel formulation. The few organogels that have been investigated for drug delivery have yielded interesting results, and it is hoped that some of these will make it to the market and improve drug therapy for the benefit of patients.

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